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09/922,490	08/03/2001	Richard J. Cristiano	INRP:021USC1	8065

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EXAMINER	
NGUYEN, DAVE TRONG	
ART UNIT	PAPER NUMBER
1632	

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7

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/922,490	Cristiano
Examiner	**Art Unit**
Dave Nguyen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Dec 26, 2002*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-16* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 4
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Claims 1, 6, 7 have been amended, claim 16 has been added by the amendment filed December 26, 2002.

Applicant's election without traverse of the species of cisplatin and viral infection in the response filed December 26, 2002 is acknowledged.

Claims 5, 11, 14, 15, 17, 18, and 20 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claimed invention.

Claims 1-16 drawn to the elected species are pending for examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification is only enabling for:

I) A method for enhancing the expression of a transgene in a target neoplastic cell *in vivo* comprising:

(a) administering a DNA-damaging agent to a subject containing a target neoplastic cell; and

(b) transferring said transgene into said target neoplastic cell between 1-4 days after said administering step;

II) A method for enhancing the expression of a transgene in a target neoplastic cell *in vitro* comprising:

(a) contacting said target neoplastic cell with a DNA-damaging agent;

(b) transferring said transgene into said neoplastic cell between about 1-4 days after said contacting step, whereby expression of the transgene is enhanced as the result of the treatment

of said target neoplastic cell with said DNA-damaging agent; and

III) The method of II, wherein said DNA-damaging agent is removed from said cell and wherein said transgene is transferred into said target cell between about 1-3 days after removing said DNA damaging agent.

The specification does not reasonably provide enablement for:

1) *In vitro* and/or *in vivo* method for enhancing the expression of a transgene in target cells other than neoplastic cells by using any DNA-damaging agent.

2) A method for enhancing the expression of a transgene *in vivo* wherein the step of removing a DNA damaging agent from an *in vivo* target cell treated with the DNA damaging agent is employed; and

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The present pending claims encompass improved gene transfer methods, both *in vitro* and *in vivo* (see the abstract or page 7 of the specification). The specification states the last paragraph of page 6:

"The present invention relies on the observation that treatment of neoplastic cells with DNA-damaging agents, prior to transduction with a transgene, results in the enhanced expression of the transgene. This effect is not observed when the cell is not neoplastic, *i.e.,* when the cell exhibits normal growth control".

The application indicates and demonstrates that prior *in vitro* treatments of host cells with a DNA-damaging agent followed by the steps of removing the DNA-damaging agent from the host cells and transfecting the host cells with a transgene, result in improved expression of the transgene when compared to simultaneous or subsequent treatment with a DNA-damaging agent, or no DNA-damaging agent at all (page 7, second paragraph; Example 1, pages 38-44; and Example 2, pages 45-50). With respect to *in vivo* gene transfer methods, the specification provides factual evidences demonstrating *in vivo* cisplatin (CDDP)-induced enhancement of

transgene expression, wherein the step of removing the DNA-damaging agent from cells contacted with the DNA damaging agent is not employed, and wherein the transfection step is employed at 0, 2, 4, and 6 days following an intraperitoneal injection of CDDP to nude mice (pages 40 and 41, for example). In addition, the specification provides evidence showing *in vitro* sensitizing effectors of DNA damaging agents other than cisplatin (etoposide (VP-16), and ionizing radiation) when a gene transfection step was employed at 0, 2, 4 days following the washing of tumor cells contacted by the DNA-damaging agent. Regarding claims drawn to a method for enhancing expression of a transgene in a host cell *in vitro,* the specification states that the step of removing a DNA-damaging agent from a host cell is accomplished by washing DNA-damaging agent-incubated cells with a buffer solution prior to the transfection step 9page 39, lines 12 and 13). More specifically, the specification on page 7 states that "it is the present inventors' observations, however, that by using a particular order and using particular timing, transgene expression may be enhanced over that observed with other protocols". Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

With respect to the scope of the claimed invention drawn to target cells other than neoplastic cells, it is not apparent how one skilled in the art reasonably correlates between enhanced gene expression in neoplastic cells pretreated with DNA-damaging agents and enhanced gene expression in other target cells pretreated with DNA-damaging agents, particularly given applicant's statements on page 6 of the as-filed specification, and given the Son *et al.* reference (PNAS, Vol. 91, pp. 12669-12672, 1994) which explicitly teaches that "muscles of the cisplatin-treated animals did not express higher CAT activity than the muscles from control uninjected animals", and that "the enhanced sensitivity to lipofection seems to be limited to the tumor cells of the cisplatin-treated animals" (pages 12671, column 2, third paragraph). It also

appears from the as-filed specification and the Son reference that the timings between the contacting step and the gene transfer step is essential for the practice of the claimed invention, and that there exist a complexity and/or complex interactions exhibited between a DNA-damaging agent and its subsequent function in effecting a gene transfer step, particularly since Son *et al.* (states that when a DNA-damaging agent is administered to a tumor *in vivo* one week prior to an *in vivo* gene transfer step, "only cisplatin could significantly sensitize the tumor for *in situ* lipofection", and that "other anticancer drugs" including etoposide, cytosine arabinonucleoside, doxorubicin, viscrastine, transplatin, and carboplatin had no effects (page 12671, column 2, second paragraph). As such and given the doubts from the art of record as to how DNA-damaging agents effect an enhanced expression of a transgene in cells other than neoplastic cells, it is not apparent how a skilled artisan reasonably extrapolates from the results of the disclosure, which are clearly within the context of tumor/neoplastic cells and of particular timings, to the entire breadth of the claimed invention, which clearly contemplates that enhanced transfection will occur in any cell including muscle cells when using the methods as claimed.

As to the *in vivo* gene transfer methods as encompassed by the presently pending claims, wherein the step of removing DNA-damaging agents from cells contacted by the DNA-damaging agents is employed, the nature of the invention drawn to *in vivo* gene transfection methods requires one skilled in the art to actively practice the removal of a DNA-damaging agent (cisplatin or ionizing radiation, for example) from a target tumor cell contacted by the DNA-damaging agent. However, neither the specification nor its incorporated references provide sufficient guidance and/or factual evidence as to how the *in vivo* removal step is employed without undue experimentation by a skilled artisan. Note that the step of stopping an *in vivo* administration of DNA-damaging agents to an animal prior to the *in vivo* gene transfer step is not the same as the step of actively removing contacted DNA-damaging agents from target tumor cells of the animal.

Thus, it is not apparent how one skilled in the art reasonably extrapolates from the guidance and/or working examples of the specification to the full scope of the claimed invention,

without undue experimentation, particularly in view of the nature of the claimed invention and the reasons indicated above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and claims dependent therefrom are indefinite in the recitation of "a method for enhancing the expression of a transgene" because it is not apparent as to exactly where the "the expression of a transgene" occurs.

The recitation of "said trasngene is a tumor suppressor" in claim 9 is indefinite because it is not apparent how a transgene which is a DNA sequence is a tumor suppressor. While the "tumor suppressor" is a protein product which is encoded by the DNA sequence, the tumor suppressor is neither the DNA sequence nor the transgene.

In claim 12, the term 'the CMV IE promoter" lacks an antecedent basis because not all CMV IE promoters known in prior art are identical in their structural sequences, and thus, it is not apparent as to which of the CMV IE promoters the term "the CMV IV promoter" refers to.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-15 are rejected under 35 USC 102(a) as being anticipated by, or in the alternative, under 35 USC 103(a), as being unpatentable over Nguyen, Dao *et al.* (Proceedings of the American Association for Cancer Research, Vol. 37, Vol. 37, #2370, March 1996)

Dao Nguyen *et al.* teaches that cisplatin (CDDP)-treated cells had 35% to 61% further inhibition of growth 3 days following p53 gene transfer compared to cells without prior CDDP treatment (abstract). More specifically, Dao Nguyen *et al.* state that the timing of administration of a DNA damaging agent (CDDP) relative to gene transfer is critical as simultaneous injection of CDDP and intratumoral AdV/CMV/p53 injections resulted in a lower therapeutic efficacy (abstract), and that a combination of sequential injection of CDDP and intratumoral injections of Adv/CMV/p53 given 2, 4, 6 days following injection of CDDP resulted in a profound inhibition of tumor growth (abstract).

Absent evidence to the contrary, the method of Dao Nguyen anticipates, or in the alternative, renders the claimed invention *prima facie* obvious.

Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alexander *et al.* (US Pat No. 5,604,090) taken with Nguyen, D. *et al.* (Proceedings of the American Association for Cancer Research, Vol. 37, Vol. 37, #2370, March 1996).

Claims 1-16 encompasses a method for enhancing the expression of a transgene encoded by an adeno-associated virus (AAV) vector in dividing and non-dividing cells *in vitro,* the method comprises contacting a target cell with a DNA-damaging agent; washing the DNA-damaging agent-incubated cells with a buffer solution; and transferring said AAV vector into the cells between about 1-3 days after removing said DNA-damaging agent.

Alexander *et al.* teach a method for enhancing the expression of a transgene encoded by an adeno-associated virus (AAV) vector in dividing and non-dividing cells *in vitro,* the method comprises contacting a target cell with a DNA-damaging agent; washing the DNA-damaging agent-incubated cells with a buffer solution; and transferring said AAV vector into the cells after the washing step, *e.g.,* column 11 bridging column 12; column 13 bridging column 14, especially lines 62-66 of column 13. Column 6, lines 31-47, and claim 19 on column 16 state that the DNA-damaging agents include cisplatin. Alexander *et al.* explicitly indicate on lines 33-35 of column 9 and lines 62-66 of column 13 that DNA-damaging-incubated cells were washed twice with fresh medium prior to vector addition. On column 11, lines 61-64, Alexander *et al.* teach that an AAV transfection step can be employed 8 hours after exposing target cells to radiation. Transfection vector wherein the SV40 polyadenylation signal sequence is also disclosed on column 8, lines 37-40. Alexander *et al.* do not teach the limitation of "between about 1-3 days" after the removal step, nor do Alexander *et al.* teach that the dividing cell is a tumor cell and/or the transgene is a p53 encoded DNA operably linked to a CMV promoter.

However, at the time the invention was made, Dao Nguyen *et al.* teaches that cisplatin (CDDP)-treated cells had 35% to 61% further inhibition of growth 3 days following p53 gene transfer compared to cells without prior CDDP treatment (abstract). More specifically, Dao Nguyen *et al.* state that the timing of administration of a DNA damaging agent (CDDP) relative to gene transfer is critical as simultaneous injection of CDDP and intratumoral AdV/CMV/p53 injections resulted in a lower therapeutic efficacy (abstract), and that a combination of sequential injection of CDDP and intratumoral injections of Adv/CMV/p53 given 2, 4, 6 days following injection of CDDP resulted in a profound inhibition of tumor growth (abstract).

It would have been obvious for one of ordinary skill in the art to have modified the gene transfer method of Alexander *et al.* by employing the gene transfer step 2, 4, 6 days following the removal step in order to enhance the expression of the trasngene in target cells *in vitro.* One of ordinary skill in the art would have been motivated to have employed the timing period as taught in Dao Nguyen in order to enhance expression of transgene in DNA-damaging treated cells, particularly since Dao Nguyen teaches that the timing of administration of a DNA damaging agent (CDDP) relative to gene transfer is critical for the improved expression of a transgene, and that a combination of sequential injection of CDDP and intratumoral injections of Adv/CMV/p53 given 2, 4, 6, days following injection of CDDP resulted in a profound inhibition of tumor growth (abstract).

It would also have been obvious for one of ordinary skill in the art to have employed the gene transfer method of Alexander *et al.* taken with Nguyen, D. *et al.* in any tumor cell, *e.g.,* cisplatin sensitive tumor cell and/or cisplatin non-sensitive tumor cells. One of ordinary skill in the art would have been motivated to have employed the gene transfer method of Alexander *et al.* taken with Nguyen, D. *et al.* in any tumor cell because Dao Nguyen teaches that gene expression in tumor cells can be enhanced when the tumor cells are pre-treated with a DNA-damaging agent.

It would also have been obvious for one of ordinary skill in the art to have employed any transgene including the p53 encoded DNA and any promoter operably linked to the DNA in the gene transfer method of Alexander *et al.* taken with Nguyen, D. *et al.* One of ordinary skill in the art would have been motivated to have employed any suitable promoter including a CMV promoter and the encoded p53 DNA in the gene transfer method of Alexander *et al.* because Alexander *et al.* teach that any gene of interest and/or any promoter suitable for AAV gene transfer methods can be employed, and because Nguyen, D. teach that a combination use of a DNA-damaging agent and a DNA construct comprising a CMV promoter and a p53 encoded DNA sequence is effective for use to demonstrate the elevation of gene expression and/or inhibition effects of growth in tumor cells which do not contain the wild-type p53 gene.

Thus, the claimed invention as a whole was *prima facie* obvious over the prior art.

Claims 1-15 are rejected under 35 U.S.C. 102(e) as being anticipated by, or in the alternative, under 35 USC 103(a) as being unpatentable over Roth *et al.* (US Pat No. 5,747,469).

The claims encompass a method for enhancing the expression of a transgene encoded by a vector in neoplastic cells, the method comprises contacting a target neoplastic cell with a DNA-damaging agent; and transferring the vector into the cells about 24 hours after said contacting step.

Roth *et al.* teach a method for killing tumor cells *in vitro* which comprises contacting a target tumor cell with a DNA-damaging agent, and transferring a vector comprising a CMV-IE promoter operably linked to a p53 encoded DNA to the tumor cell within about 12-24 hours after the contacting step, *e.g.,* column 7, lines 40-55, and column 4, lines 1-35. More specifically, Roth *et al.* teach that in embodiments where the DNA damaging factor and p53 are applied separately to target cells, one would generally ensure that a significant period of time did not expire between the time of each delivery, such that the DNA damaging agent and p53 would still be able to exert an advantageously combined effect on the cell (column 4, second paragraph). DNA damaging agents including cisplatin (CDDP) are disclosed on columns 4 bridging column 5. Gene transfer techniques including adenoviral transfection are disclosed on column 5. Adenoviral vectors containing a human CMV IE promoter operably linked to the p53 encoded DNA are disclosed on columns 24 and 25. The SV40 signal sequence is also disclosed in Example 1 (column 22). More specifically, Roth *et al.* states:

> "[I]n embodiments where the DNA damaging factor and p53 are applied separately to the cell, one would generally ensure that a significant period of time did not expire between the time of each delivery, such that the DNA damaging agent and p53 would still be able to exert an advantageously combined effect on the cell. In such instances, it is contemplated that one would contact the cell with both agents within about 12-24 hours of each other"

Thus, Roth anticipates the claimed invention, or the alternative, render the claimed invention *prima facie* obvious, particularly when the limitation is directed to about 24 hours.

Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roth *et al.* (US Pat No. 5,747,469) taken with Alexander *et al.* (US Pat No. 5,604,090).

The claims encompass a method for enhancing the expression of a transgene encoded by a vector in dividing and non-dividing cells *in vitro,* the method comprises contacting a target cell with a DNA-damaging agent; washing the DNA-damaging agent-incubated cells with a buffer solution; and transferring the vector into the cells between about 1-3 days after removing said DNA-damaging agent.

Roth *et al.* teach a method for killing tumor cells *in vitro* which comprises contacting a target tumor cell with a DNA-damaging agent, and transferring a vector comprising a CMV-IE promoter operably linked to a p53 encoded DNA to the tumor cell within about 12-24 hours after the contacting step, *e.g.,* column 7, lines 40-55, and column 4, lines 1-35. More specifically, Roth *et al.* teach that in embodiments where the DNA damaging factor and p53 are applied separately to target cells, one would generally ensure that a significant period of time did not expire between the time of each delivery, such that the DNA damaging agent and p53 would still be able to exert an advantageously combined effect on the cell (column 4, second paragraph). DNA damaging agents including cisplatin (CDDP) are disclosed on columns 4 bridging column 5. Gene transfer techniques including receptor-mediated internalization and adenoviral transfection are disclosed on column 5. Adenoviral vectors containing a human CMV IE promoter operably linked to the p53 encoded DNA are disclosed on columns 24 and 25. The SV40 signal sequence is also disclosed in Example 1 (column 22). Roth *et al.* do not teach the step of removing DNA-damaging agents from cells contacted with the DNA-damaging agents.

However, at the time the invention was made, Alexander *et al.* provide detailed teaching on lines 33-35 of column 9 and lines 62-66 of column 13 disclosing that DNA-damaging-incubated cells were washed twice with fresh medium prior to vector addition. On column 11, lines 61-64, Alexander *et al.* teach that an AAV transfection step can be employed 8 hours after exposing target cells to radiation.

It would have been obvious for one of ordinary skill in the art at the time the invention was made to have employed the removal step in the gene transfer method of Roth *et al.* One of

ordinary skill in the at would have been motivated to have employed the washing step, as taught in Alexander *et al.,* in the gene transfer method of Roth *et al.* because the washing step would naturally ensure that the added vector DNA are not degraded and/or damaged by DNA damaging agents contained in the solution or bound to the surface of the target cells.

It would also have been obvious for one of ordinary skill in the art at the time the invention was made to have employed the transfection step at between to 1-3 days after the removal step, as taught by Roth *et al.* taken with Alexander *et al.* One of ordinary skill in the art would have been motivated to have employed the transfection step at between about 1-3 days after the removal step because Roth *et al.* teach that in embodiments where the DNA damaging factor and p53 are applied separately to target cells, one would generally ensure that a significant period of time did not expire between the time of each delivery, such that the DNA damaging agent and p53 would still be able to exert an advantageously combined effect on the cell.

Thus, the claimed invention as a whole was *prima facie* obvious over the prior art.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-15 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,271,207. Although the conflicting claims are not identical, they are not patentably distinct from each other because both set of claims encompass the subject matter drawn to:

A method for enhancing the expression of a transgene in a target neoplastic cell *in vivo* comprising:

(a) administering a DNA-damaging agent to a subject containing a target neoplastic cell; and

(b) transferring said transgene into said target neoplastic cell between 2-4 days after said administering step.

Thus, the examined claims the claims of the US patent are obvious variants of one another.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

DAVE T. NGUYEN
PRIMARY EXAMINER